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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

October 25, 2000

Docket No. 00D-1418

Gentlemen:

Enclosed are two copies of my comments on the draft ICH document "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients". The comment period closed October 2, 2000 but I hope my comments, although officially late, will be considered.

I also would like to take this opportunity to voice a complaint about the shortness of time for comment, 60 days. The later time period is simply too short for the working public to make comments. Not all ICH draft guides have this short a comment period but the 60 day period is usually used when FDA must attend an ICH meeting at which the guide will be discussed only a few months after publication of the draft ICH guide. In this case, it is the ICH Meeting 5 in San Diego, November 9-11, 2000. This short comment period coupled with an even shorter time FDA has to review and assimilate the comments is a disservice to the public who not only follow these developments but may be bound by them.

I recommend no less than a 90 day comment period for any guide but especially for ICH guides. If that doesn't provide enough time for FDA to discuss the guide at an ICH meeting, then FDA should wait until the next ICH meeting for the discussion.

Very truly yours,

Robert A. Jerussi

Robert A. Jerussi, Ph.D.
President

cc: Dr. Jane Henney

00D-1418

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Comments on the Step 2 ICH Document on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

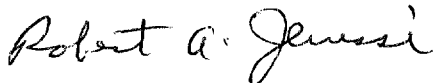
This is a very thorough and broad guide that covers all aspects of API production. However, it is too broad and includes intermediates production. The definition of a starting material presented in 1.3 seems adequate but there are at times steps in a synthesis that produce intermediates that do not need to be covered by GMPs. Not all intermediates in a synthesis need GMP type controls as pictured in the Table on page 3 of the draft guide under Chemical Manufacturing. Only those intermediates that can be designated as critical, penultimate, or the one just before the step that produces the API need this type of control.

The stress on GMP coverage for all steps of a synthesis mimics what is done in the production of a drug product but the two processes are vastly different and there should be different types of GMP concerns for each. This is because the process of manufacturing a drug product is one of contamination control e.g. preventing contamination whereas the process of manufacturing a drug substance is one of purification. If during the manufacture of a drug product, contamination is introduced early on, it is difficult if not impossible to correct. This is not true of a chemical synthesis where purification occurs at various steps of the synthesis and with the crude API.

Another huge difference in the manufacture of an API and a drug product is that the ingredients in the former are meant to chemically react whereas the ingredients in the production of a drug product are not meant to interact e.g. be inert. Thus there are unreacted materials and reaction products not necessarily intended in the manufacture of a drug substance but which are not found in the production of a drug product since a set formula is used for each ingredient. That is why purification is such an important component in the production of an API.

Significantly, the draft document contains a Section 8. Production and In-Process Controls which has a subsection 8.5 on Contamination Control but does not contain one on purification!

Recommendation: That those parts of this draft guide that deal with the actual production of an API be revised to be specific for that type of production and not simply copy what is now applied to the production of a drug product.



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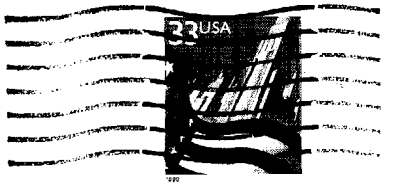

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